The I_{Ks} activator DHA can normalize repolarization in congenital long QT type 2 transgenic rabbit models in a genotype-specific fashion

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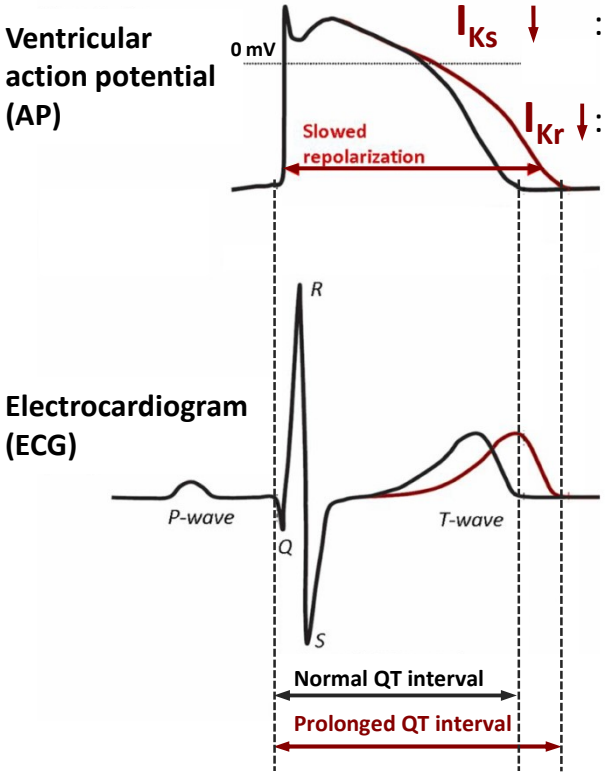
Long QT syndromes

INTRODUCTION:

Human Long QT syndrome (LQT1-16): genetic cardiac channelopathy, prevalence ~ 1: 10 000 [1,2]



Reduced currents

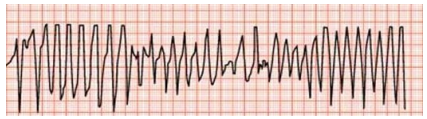
I_{Ks} : slow delayed rectifier K^+ → LQT5: KCNE1 (β subunit)

I_{Kr} : rapid delayed rectifier K^+ → **LQT1: KCNQ1 (α subunit)**, → **LQT2: KCNH2 (α subunit)** } ~ 80% of all LQTS

↓

Prolonged QT interval

↓



Torsades de Pointes (TdP)

↓

Sudden cardiac death (SCD)

Therapy: beta-blockers fail to prevent arrhythmias in ~30% of the patients[1,2]

↓

Novel therapeutic strategies are needed![3]

[1]Priori SG Europace 2015; [2]Schwartz PJ Circ Arrhythm Electrophysiol 2012; [3]Cho Y Korean Circ 2016

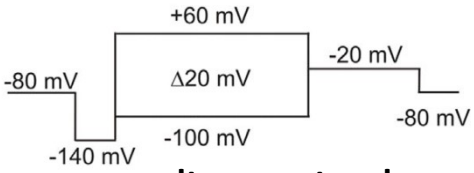
DHA and its effects on I_{Ks}

INTRODUCTION:

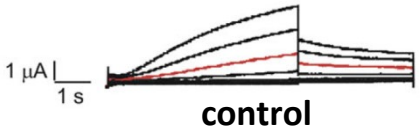
DHA (docosahexaenoic acid): a polyunsaturated ω-3 fatty acid, its *in vitro*[4] and *ex vivo*[5] **I_{Ks} –activating** effects have been described

Effect of DHA on KCNQ1/KCNE1 channels expressed in *Xenopus oocytes*

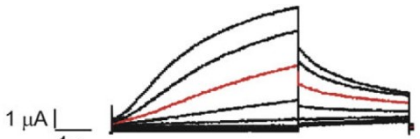
Measurement of I_{Ks}



voltage protocol

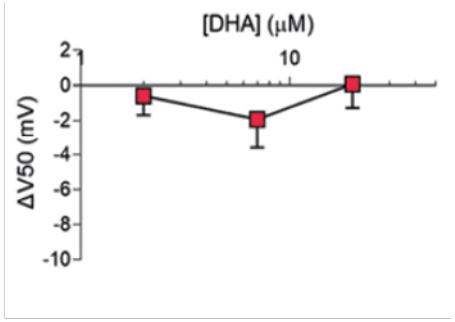


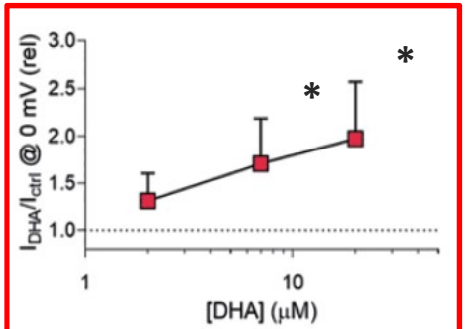
control



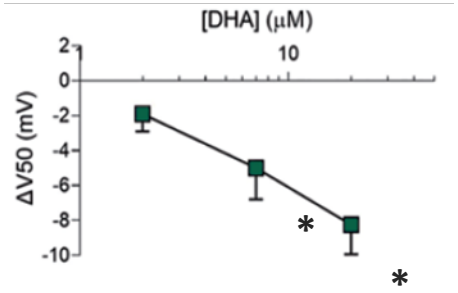
20 µM DHA

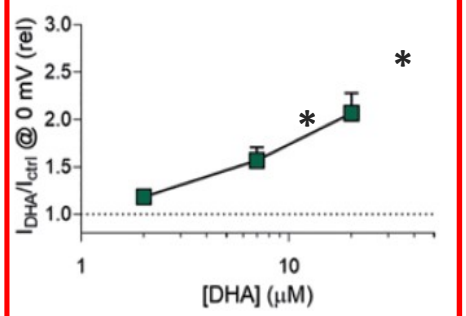
DHA effect on <u>human</u> KCNQ1/KCNE1 (I_{Ks})





DHA effect on <u>rabbit</u> KCNQ1/KCNE1 (I_{Ks})



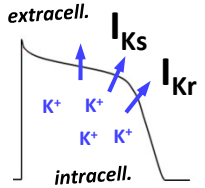


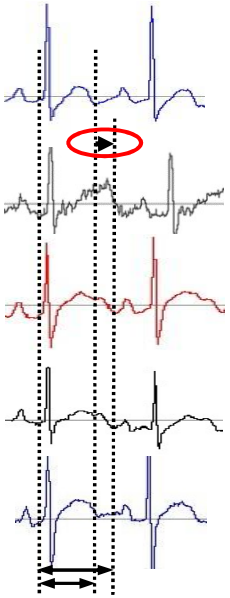
[4]Liin SI Cell Rep 2018; [5]Skarsfeldt MA Acta Physiol 2020

Transgenic LQT rabbit models

MODELS:

Transgenic LQTS rabbit models: cardioselective overexpression of human LQTS-causing loss-of-function mutants of cardiac K^+-channel coding genes →‚dominant negative' effect →human LQTS-like phenotype



	mutation(s); affected ion current(s)	ECG	Main features
Wild type (WT)	none		➢ normal phenotype
LQT1 (Brunner et al. 2008)	KCNQ1-Y315S; I_{Ks}		➢ manifest LQTS, provoking factors → TdP/SCD[6]
LQT2 (Brunner et al. 2008)	HERG-G628S; I_{Kr}		➢ manifest LQTS, spontaneus TdP/SCD[6]
LQT2-5 (Hornyik et al. 2020)	as LQT2&LQT5; I_{Kr}+I_{Ks}		➢ similar to LQT2[7]
LQT5 (Major et al. 2016)	KCNE1-G52R; I_{Ks}		➢ hidden LQTS, high sensitivity to QT prolongation[8]

QT

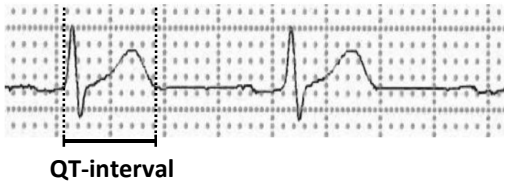
AIM: to study the potential repolarisation normalizing effect of DHA in transgenic LQTS rabbit models

[6]Brunner M The J. of Clin Inv 2008; [7]Hornyik T British J. of Pharm 2020; [8]Major P British J. of Pharm 2016

Methods

METHODS:

in vivo: telemetric & 12-lead ECG



Effect of DHA (docosahexaenoic acid) on:

- ✓ **QTc**: heart rate corrected QT time
- ✓ **STV_{QT}**: ‚beat-to-beat' short term variability of QT
- ✓ **QT dispersion**: max. difference of QT-s measured in 12-lead

Protocols:

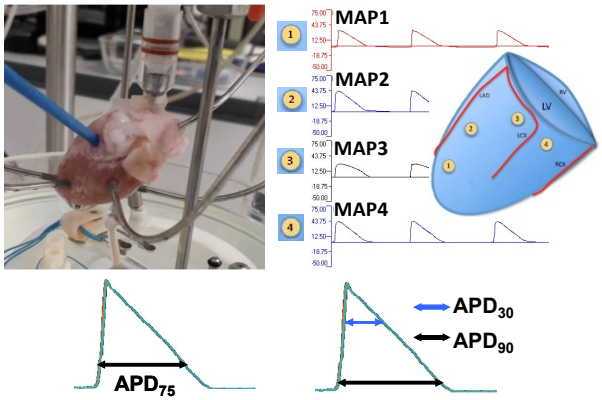
- **telemetric ECG**

1st day *2nd day*

- **12-lead ECG**

10 min *20 min*

ex vivo: monophasic action potential (MAP)



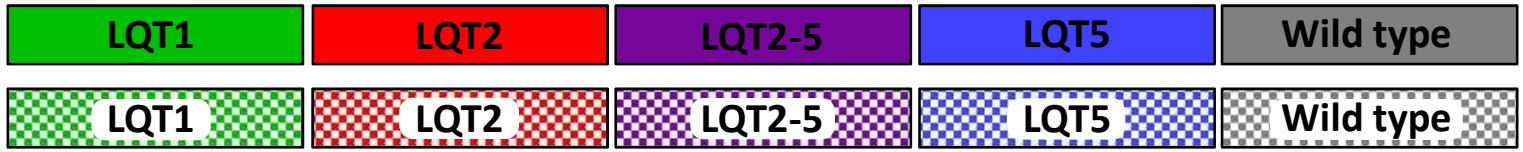
Langendorff-perfused AV-ablated hearts, stimulated at 2Hz

- ✓ **APD_{75}**: duration of AP at 75% of repolarisation
- ✓ **APD_{90-30}**: triangulation of AP, proarrhythmia marker
- ✓ **APD_{75} dispersion**: regional difference of AP duration

Protocol:

10 min *10 min*

Groups:

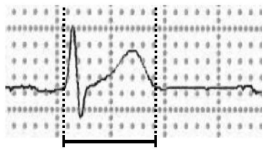


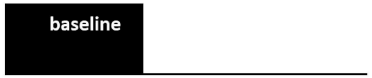
Repolarisation normalizing effects of DHA in LQT2 rabbit models

RESULTS:

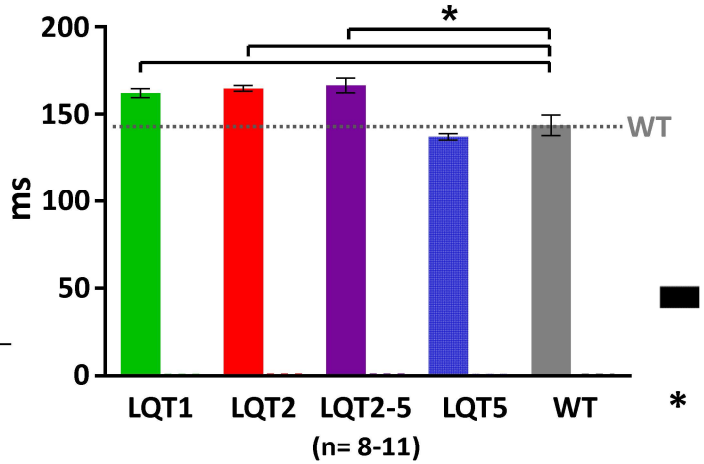
Baseline ECG characteristics:

in vivo: telemetric ECG





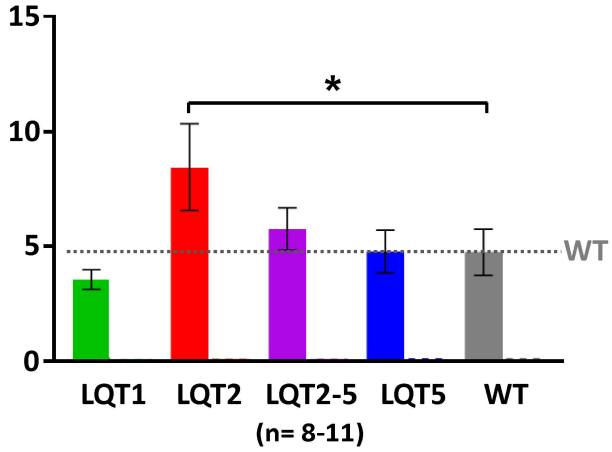
QTc



Baseline

* p < 0.05

STV_{QT}



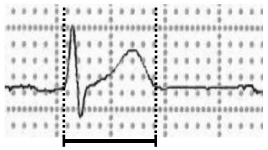
At baseline, LQT1, LQT2 and LQT2-5 exhibited prolonged QTc, and LQT2 showed elevated STV_{QT} compared to WT.

Repolarisation normalizing effects of DHA in LQT2 rabbit models

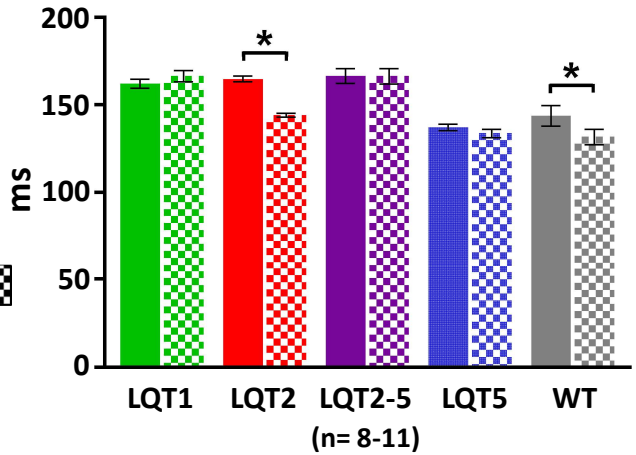
RESULTS:

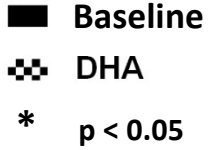
Effect of DHA (docosahexaenoic acid) on:

***in vivo*: telemetric ECG**

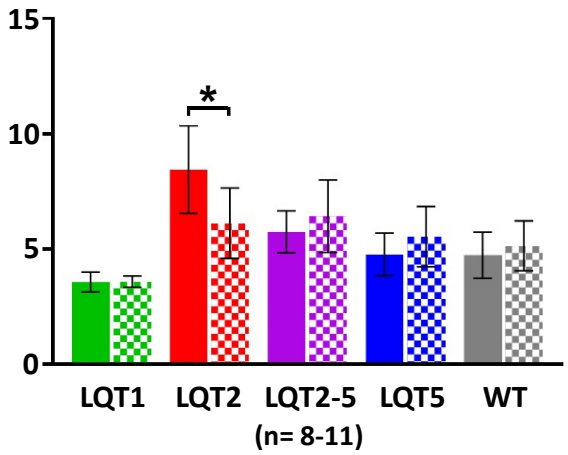


QTc

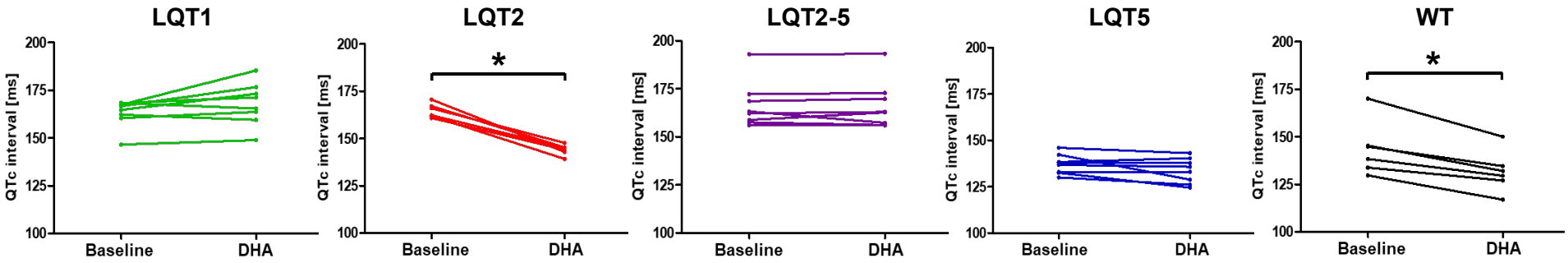




STV_{QT}



Individual QTc changes



DHA administration shortened QTc in LQT2 and WT, and decreased STV_{QT} in LQT2.

Repolarisation normalizing effects of DHA in LQT2 rabbit models

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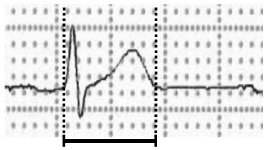
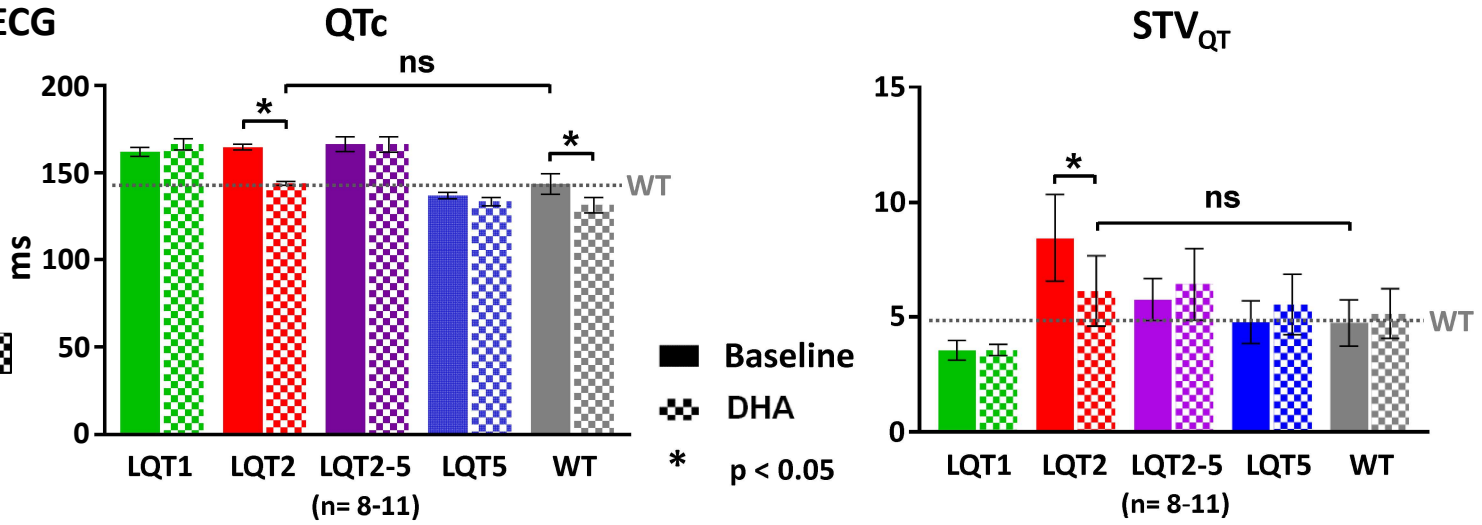




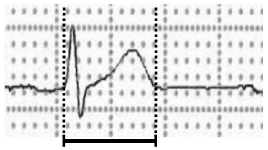
DHA-induced QTc and STV$_{QT}$ shortening led to complete normalization of the LQT2 phenotype.

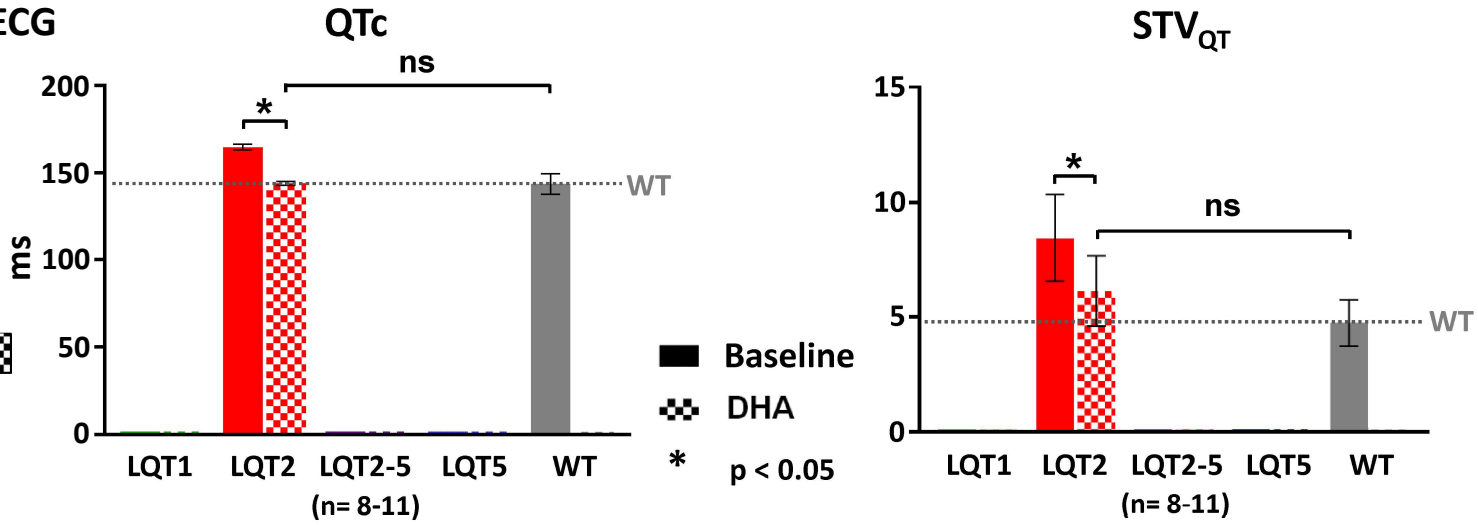
Repolarisation normalizing effects of DHA in LQT2 rabbit models

RESULTS:

Effect of DHA (docosahexaenoic acid) on:

***in vivo*: telemetric ECG**





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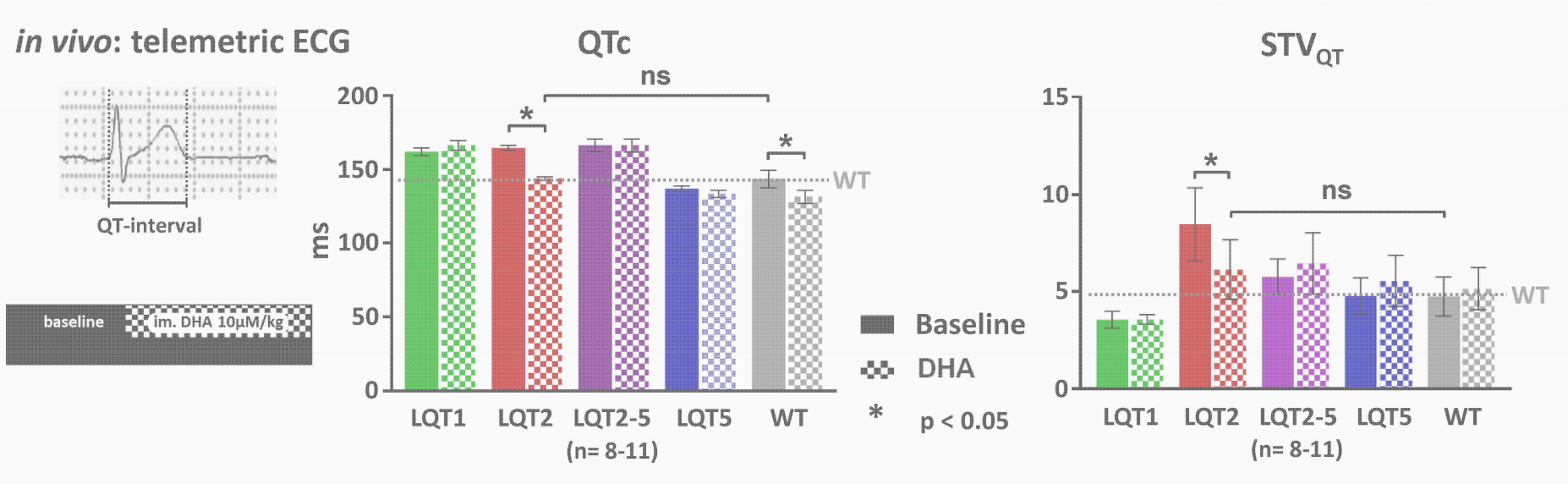
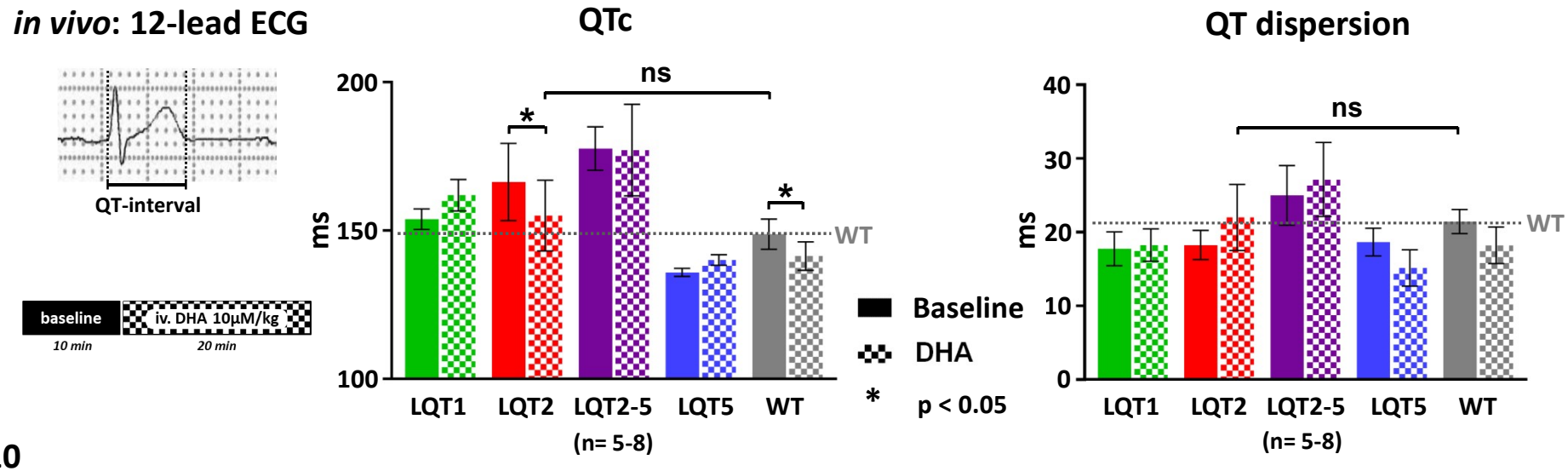
Repolarisation normalizing effects of DHA in LQT2 rabbit models

RESULTS:

Effect of DHA (docosahexaenoic acid) on:



DHA administration did not increase QT disperson in any genotype!

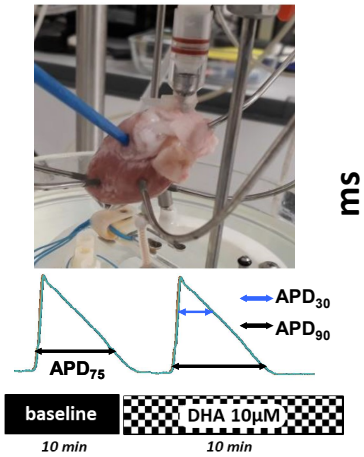


Repolarisation normalizing effects of DHA in LQT2 rabbit models

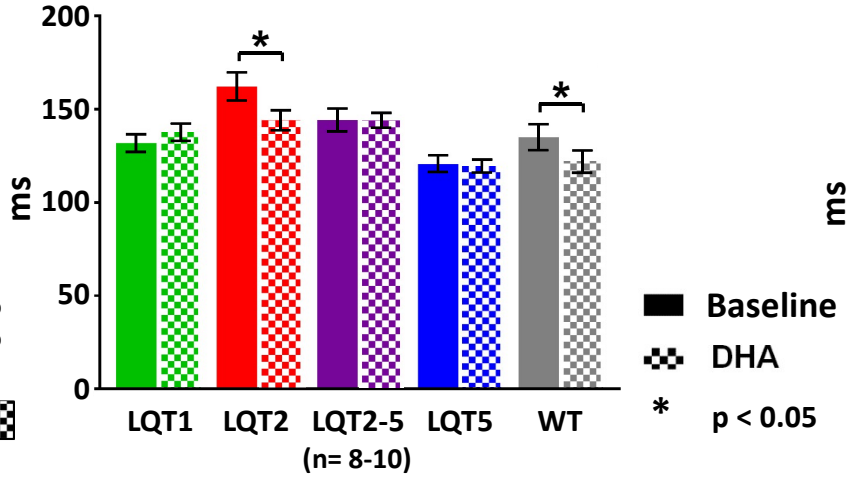
RESULTS:

Effect of DHA (docosahexaenoic acid) on:

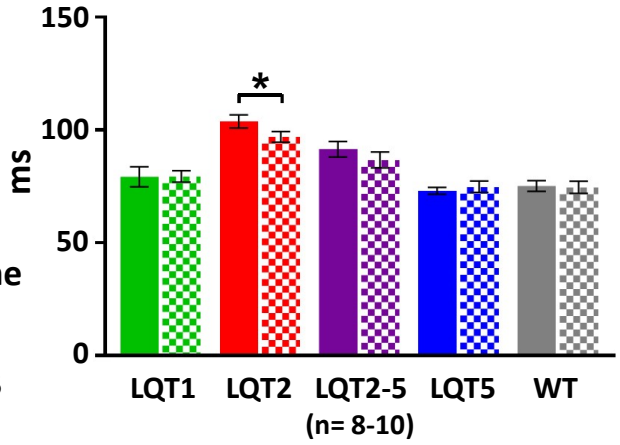
***ex vivo*: MAP**



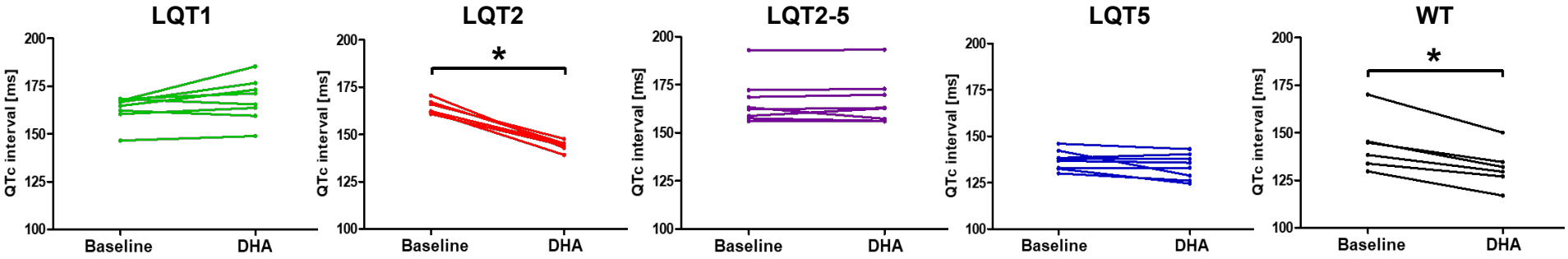
APD_{75}



APD_{90-30}



Individual APD_{75} changes



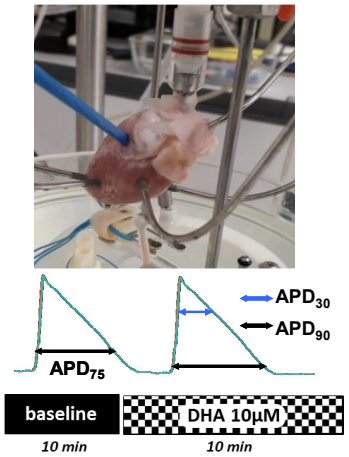
DHA administration shortened APD_{75} in LQT2 and WT, and decreased APD_{90-30} in LQT2.

Repolarisation normalizing effects of DHA in LQT2 rabbit models

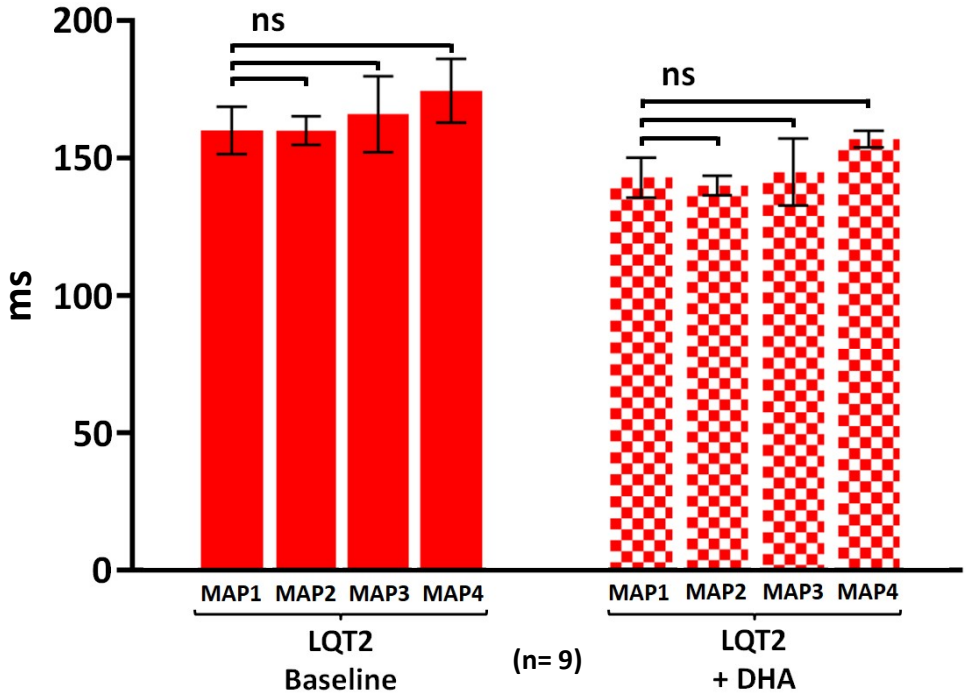
RESULTS:

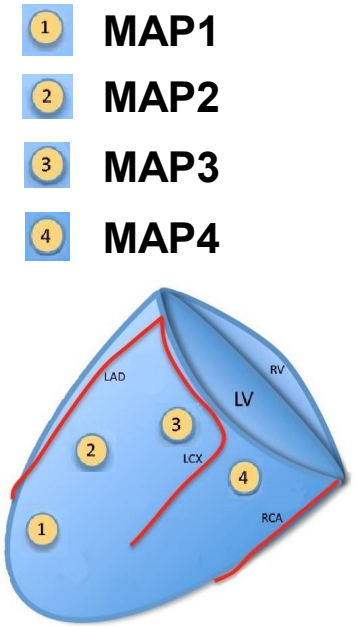
Effect of DHA (docosahexaenoic acid) on:

***ex vivo*: MAP**



Regional heterogeneity of the AP duration in LQT2 hearts





DHA did not increase regional AP duration heterogeneity!

Repolarisation normalizing effects of DHA in LQT2 rabbit models

SUMMARY:

Administration of DHA exhibited beneficial repolarisation shortening effect through activation of I_{Ks} **in LQT2**:

- completely **normalized QT** interval and **STV_{QT}**
- **shortened AP duration** and reduced **AP triangulation** (APD_{90-30})
- **did not increase QT dispersion** and regional **APD heterogeneity**

DHA had no effect in LQT1, LQT5 and LQT2-5 with functionally impaired α- or β-subunits to I_{Ks}.

DHA could thus represent a novel therapeutic tool in LQT2 syndrome.

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University of Bern, Institute of Physiology, Department of Translational Cardiology:

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NEMZETI KUTATÁSI, FEJLESZTÉSI ÉS INNOVÁCIÓS HIVATAL

MINISTRY OF HUMAN CAPACITIES

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